New and Notable

Switching Sides: The Actin/ Membrane Lipid Connection

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Cell surface membrane proteins and lipids engage underlying actin filaments in complicated ways. The players engaged are known, and it is clear that the terms of their engagement are important for membrane functions such as endocytosis and receptor-mediated signaling. However, little is known about the way membrane bilayer and membrane skeleton mutually influence one another in these functions. This is due at least in part to the large number of protein and lipid modulators of actin, notably the inositol phospholipid, phosphatidylinositol 4,5 bisphosphate, PIP2 (1). The article by Liu and Fletcher in this issue of *Biophysical Journal* (2) shows that the anchoring of actin to a bilayer containing PIP2 and subsequent growth of filamentous actin drives phase separation of lipids in a multi-component lipid vesicle. The actin filament network also stabilizes these separated domains once formed. The article highlights the importance of the inner leaflet PIP2 for the actin-mediated reorganization of lipids in both leaflets of the bilayer and informs the debate on coupling lipid domains of inner and outer bilayer leaflets. The simplified model system and some careful controls isolate just one of the many functions of PIP2 in whole cells (3)—the linking of bilayer lipids to actin through PIP2-binding proteins, in this case N-WASP. The data of Liu and Fletcher suggest a way of understanding why actin is important for receptor-mediated signaling and how it may connect to membrane lipid domains. However, the data also yield a surprise as to just which lipid domains are stabilized actin networks, and they may alter thinking about receptor-mediated signaling and lipid domains.

The surprise comes because Liu and Fletcher show that the actin/N-WASP/PIP2 connection is by way of domains rich in unsaturated and short-chain lipids, l_d domains. On the other hand, the lipids most important to receptor-mediated signaling seem to be those of ''lipid rafts'', cholesterol-rich so-called l_o domains. Still, the ''anti-raft'' effects of filamentous actin networks ought to stabilize l_o as well as l_d domains, if only by excluding them from stabilized l_d domains. The view recognizes rafts as just one of many types of membrane lipid domains (4) and one whose organization can be affected by changes in ''nonraft'' structures. The model system results also lead us to understand how PIP2, not a raft lipid, might be important for raft-dependent signaling, for example from the epidermal growth factor receptor (5). The results also tie to observations that actin polymerization consequent to receptor ligation is important for coalescence of raft lipids around the T-cell receptor and enhancement of signaling (6,7). A similar argument can be made for signaling from the Fcε receptor (the IgE receptor), where again there is some complicated association between actin filaments and receptor entry into rafts. On the other hand, some recent results on the B-cell receptor for antigen (membrane-bound immunoglobulin) suggest that actin depolymerization enhances signaling and raft clustering (8). I suppose that this last observation can be interpreted by inverting the view of domain formation in Liu and Fletcher (2).

For all that the new work offers a real insight into the way in which membrane bilayer and membrane skeleton can be coupled, we need to remember that the road from liposomes to native cell membranes never runs smoothly. The speculation that ''by controlling the state of actin polymerization at the membrane, it may be possible for the cell to finely control membrane organization…'' (2) is appealing, but cells have massively parallel routes to almost every function. Still it is good to have our feet set on one of these routes to understanding the complex tangle of a functional plasma membrane.

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